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Recurrence of Stevens-Johnson syndrome/toxic epidermal necrolysis induced by allopurinol and piroxicam

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are life-threatening mucocutaneous diseases that are predominantly drug-induced. The recurrence of SJS/TEN by two unrelated drugs has been rarely reported. Herein, we report on a patient who developed SJS/TEN twice, and by using an enzyme-linked immunospot (ELISPOT) assay, the culprit drugs were confirmed to be allopurinol and piroxicam.

A 47-year-old man presented to our dermatology department in June 2018 with a 10-day history of a maculo-papular rash and erythema multiforme that had developed on his face and spread to the trunk, arms, and legs, accompanied by oral mucosal erosion. The patient had been diagnosed with hyperuricaemia and prescribed allopurinol for eight days previously. The patient was diagnosed with SJS, and he received methylprednisolone (60 mg QD for seven days, with gradual tapering), intravenous immunoglobulin (20 g QD for five days), and supportive therapy. Skin and mucosal lesions improved well, and the patient was discharged on the 15th day.

However, the patient was transferred to our emergency department from a local hospital in January 2020 and presented with a seven-day history of blister and desquamation. Although the patient was treated with methylprednisolone (250 mg QD) and intravenous immunoglobulin (20 g QD) for five days in the local hospital, the lesions still progressed rapidly. On presentation, the blisters and desquamation had developed globally along with severe conjunctiva, oral, and genital mucosal erosion. The patient exhibited more than 60% epidermal detachment (*figure 1A, B*). The patient had taken piroxicam due to an acute gout attack nine days ago. The patient was diagnosed with TEN and immediately admitted to the dermatology department, where he received methylprednisolone (80 mg QD), etanercept (25 mg, Q3D),

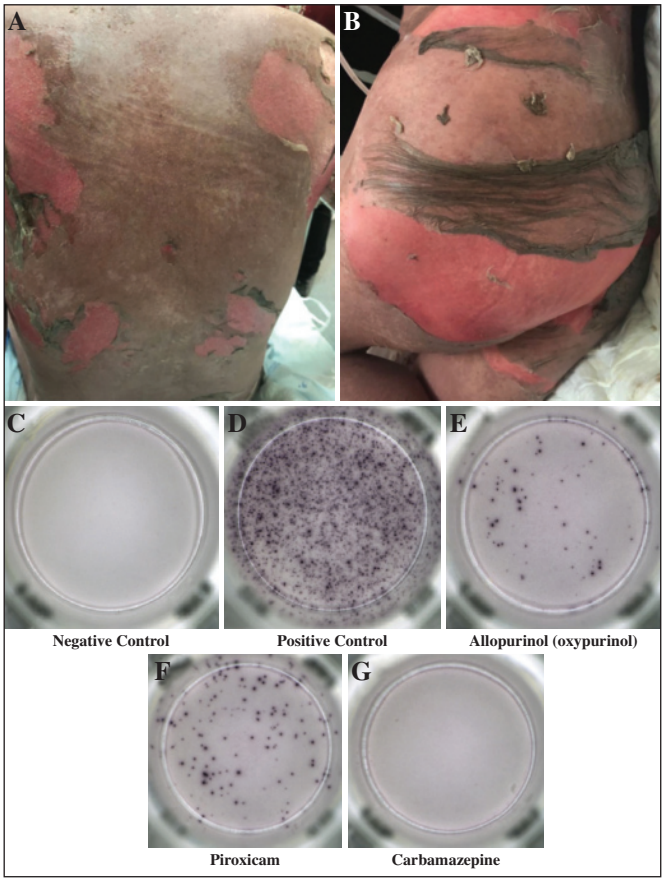

Figure 1. A, **B**) Clinical images of the patient demonstrating epidermal necrosis and sloughing. **C-G**) Drug-specifc IFN-γ responses, as demonstrated by an enzyme-linked immunospot assay.

and supportive therapy. After 16 days of hospitalization, the patient progressively exhibited full re-epithelization of skin lesions and was discharged.

To confirm the culprit drug, an IFN-γ ELISPOT assay was performed. IFN-γ ELISPOT assay is a sensitive *in vitro* test for identifying the culprit drug in SJS/TEN cases; it works by recognizing drug-specific T cells among thousands of peripheral blood mononuclear cells [1]. A significantly high number of IFN-γ spot-forming cells were observed in the positive control and upon incubation with oxypurinol (the metabolite of allopurinol) and piroxicam. No IFN-γ-secreting cells were observed in the negative control or upon stimulation with an unrelated drug, carbamazepine (*figure 1C-G*).

SJS/TEN are severe drug hypersensitivity reactions (DHR) leading to high mortality, characterized by detachment of the epidermis and erosion of the mucous membrane. At onset of DHR, the patient must not continue to receive the same or related drugs because DHR recurrence can be more severe and life-threatening. However, DHR recurrence might also be induced by unrelated drugs, which presents as a drug reaction with eosinophilia, systemic symptoms, and maculopapular exanthema, as reported previously [2, 3]. Compared with other types of DHR, the recurrence of SJS/TEN due to unrelated drugs has been seldom reported [4].

Allopurinol, a first-line drug used for treating gout, is one of the most common drugs associated with SJS/TEN. Piroxicam is an enolic derivative of the oxicam class of non-steroidal anti-inflammatory drugs (NSAIDs), and is usually associated with an increased risk of SJS/TEN. Nevertheless, the concurrent use of piroxicam might increase the risk of allopurinol-induced SJS/TEN [5]. Herein, the patient, who had a history of allopurinol-induced SJS two years ago, developed TEN on exposure to piroxicam. Therefore, in line with previous studies, we suggest that patients with a history of allopurinol-associated drug hypersensitivity reactions should be cautiously prescribed piroxicam. ■

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Late-onset cutaneous eruption in hospitalized COVID-19 patients

In the recent months of the COVID-19 pandemic, many clinical manifestations have been described [1,2]. We describe eight COVID-19 positive patients who, after having a negative nasopharyngeal swab (NPS), developed a macular exanthem with a distinct pattern. All the information regarding the patients and the timing of the rash are summarized in *supplementary table 1*.

We observed six males and two females (mean age: 65.5+/-3.1), hospitalized for COVID-19 infection; five patients were admitted to the ICU. All patients tested positive by NPS before/during their hospitalization. After establishing a negative NPS, in all patients, a cutaneous eruption was observed. The mean latency period between the onset of COVID-19 signs and symptoms and the onset of the rash was 25 days (range: 18-40 days); for this reason, it was considered a late-onset rash (*supplementary table 2*). Despite being treated with many drugs, no new drugs were introduced before the onset of the rash nor were drugs changed as a result of the rash.

Five out of eight patients already had systemic steroid therapy and in two of them, this was implemented; all the patients started systemic antihistamine (anti-H1) and topical steroid therapy. The skin findings were similar in all patients: erythematous macules and patches with jagged margins, that usually localized to the trunk, laterally and symmetrically, with involvement of neck, axillae, and groin folds, but always sparing the palmoplantar areas, face and mucosae (*figure 1*). Patients experienced mild pruritis. Lesions resolved with mild scaling.

Despite the huge number of COVID-19 studied cases, reports of dermatological diseases have been scarce. A skin rash has been reported in two out of 1,099 and three out of 1,590 patients presenting with COVID-19 disease in China [1, 2]. In Italy, Recalcati [3] reported cutaneous manifestations in 18 out of 88 COVID-19 patients, describing three main patterns: erythematous rash, urticaria, and chickenpox-like lesions. Marzano *et al*. [4] reported a varicella-like exanthem in the first 15 days of COVID-19 disease. Mahé *et al*. [5] reported a case with an erythematous rash on antecubital fossae, trunk and axillary folds. This rash appeared reminiscent of symmetric drug-related intertriginous and flexural exanthema (SDRIFE). Amatore *et al*. [6] described a rash characterized by erythematous and oedematous, annular plaques involving the trunk and arms, sparing the face and mucous membranes.

Galván Casas *et al.* [7] described 375 Spanish cases of rash related to suspected or confirmed COVID-19 and classified them into five patterns: pseudo-chilblain, vesicular eruptions, urticarial lesions, maculopapular eruptions and livedo or necrosis.

Herrero-Moyano *et al*. [8] were the first to report a series of patients with late-onset maculopapular rash, and hypothesized that this could be linked to the cytokine storm of the hyperinflammatory phase caused by the virus or drugs,

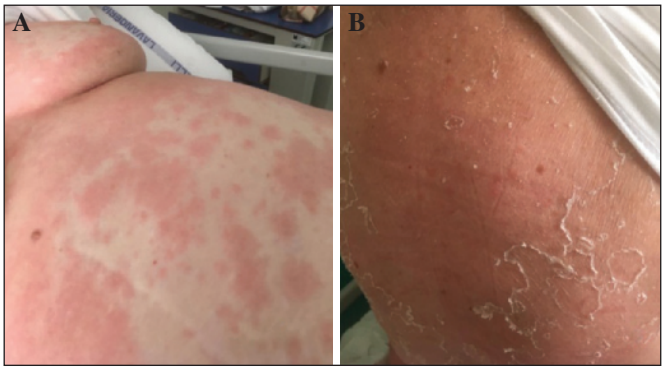

Figure 1. A) Erythematous macules and confluent patches with jagged margins, localized on the trunk and the folds (Patient 6). **B**) Mild desquamation on the back (Patient 6).